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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 051404

Application Number: 09/701,232
Filing Date: July 05, 2001
Appellant(s): LAL ET AL.

Susan K. Sather
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 02/23/04.

(1) Real Party of Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Appeal

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Groupings of Claims

Appellant's brief includes a statement that claims do not stand or fall together, but does not provide reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Vasiliauskas et al. (1999), Mechanisms of Development, Vol. 82 (1-2), pp 79-94.

Hilton et al. (1998), PNAS, USA Vol. 95, pp 114-119.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 21-29, 31-32 and 36-37 are rejected under 35 U.S.C. under 35 U.S.C. 101. This rejection is set forth in the prior Office Actions mailed on 21 February 2003 and 21 October 2003.

Claim Rejections - 35 U.S.C. §101:

Claims 21-29, 31 -32 and 36-37 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. Claims 21-29, 3 1-32 and 36-37 of the instant invention are directed to an isolated polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 5 and the polynucleotide comprising the nucleotide sequence set forth in SEQ ID NO:14 which encodes said polypeptide. The specification describes the disclosed polypeptides as being purified human SOCS proteins, (page 3, lines 20-30). Table 2 lists a number of signature sequences that the claimed polypeptide of SEQ ID NO:5 contains, and table 3 discloses that the polynucleotide of SEQ ID NO: 14 is expressed in reproductive, cardiovascular and hematopoietic/immune systems and that it is associated with cancer, inflammation and neurological disorders. However, the instant specification does not explain how the polynucleotide of SEQ ID NO: 14 is associated with these diseases. The instant specification states the claimed polypeptides contain SOCS box, however, it does not disclose any information regarding biological activity of the claimed polypeptide . Although instant specification asserts that the claimed polypeptide can be used for diagnosis, treatment or prevention of cancer, immune and neurological disorders and infectious diseases, (page 15, lines

20-24), it does not disclose how is the claimed polypeptide and polynucleotide can be used in these disparate diseases.

Suppressor of cytokine signaling family (SOCS) are recently identified inhibitors of cytokine and growth factor signaling that act through Janus kinase (JAK/signal) transducers and activators of transcription pathway. One class of said family is composed of 8 proteins (CIS, SOCS-I to SOCS-7), which contain a C-terminal SOCS box domain and a central SH2 domain. Other proteins that contain SOCS box contain WD-40 repeats, a SPRY domain or ankryn-repeat or GTPase domain N-terminal of the SOCS box, (see Hilton et al page 1 14, column 2 and figure 1). Thus it is unclear from the teachings of the instant specification which group of SOCS box containing proteins does the claimed polypeptide belong to. It is thought that SOCS- 1 plays an important role in regulating signal transduction by binding via its SH2 domain to activated JAK molecules and that CIS is thought to block STATS. However, the roles that other members of this family play have not been elucidated. Although the conservation of the SOCS box at the amino acid level appears to be important, its function is not known at the moment, (see Hilton, page I 18, bottom of column 1) and it seems that SOCS-I does not act through the SOCS box to bind to JAK. Therefore, having an SOCS box does not impart a utility common to all the proteins having this box. Furthermore, without knowing the biological activity of the claimed polypeptide, what other domains does it contain, (for example does it contain an SH2 domain which seems important for SOCS-I, does the claimed protein regulate signal transduction and if so how?), one of ordinary skill

in the art would not be able to use the claimed protein or predict an activity for said protein, simply because it comprises an SOCS box. Therefore, the claimed invention is not supported by either a substantially asserted utility, specific or a well established utility, because it is directed to polypeptide with no known activity.

Claim Rejections - 35 U.S.C. §112:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-29, 31-32 and 36-37 are also rejected under 35 U.S.C. 1 12, first paragraph. Specifically, since the claimed invention is not supported by either a substantially asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. No biological activity was assayed or determined for the claimed polypeptide or the polynucleotide encoding it. Therefore, there is no specific and substantial assertedutility or well established for the claimed polypeptide comprising the amino acid sequence of SEQ ID NO: 5 or the polynucleotide of SEQ ID NO: 14.

Should Applicants establish the physiological significance of the polynucleotide of SEQ ID NO: 14 and/or the polypeptide of SEQ ID NO:5, instant specification would still fail to adequately enable an isolated polypeptide comprising an amino acid that has at least 90% identity to the polypeptide of SEQ ID NO:5, as recited in claim 21; or an isolated polynucleotide comprising at least 90% identical to the polynucleotide of SEQ ID NO:14, as recited in claim 31. It is well known in the prior art that changes in a

nucleotide sequence can have a dramatic affect on the protein product encoded by the sequence, and that changes in the amino acid would also change the function of the protein. While the degeneracy of the genetic code accommodates some variation in the nucleotide sequence, the extent of variation disclosed go far beyond alternate codons for the same amino acid. A skilled artisan would expect that the variation in the polynucleotide sequence would at best code for a polypeptide that has impaired function and at worst be either nonfunctional or an entirely different product from that of the claimed invention. Therefore, it would be impossible to predict with certainty the effect of a substitution, insertion, or deletion of a series of nucleotides, or even one nucleotide, on the encoded product. In order to make an accurate assessment of the modifications encompassed by these claims and to determine the function of the encoded protein would require undue experimentation.

With respect to amino acid modifications, the instant specification does not provide the guidance needed to predictably alter by 10%, i.e. 42 amino acids in SEQ ID NO:5, with any reasonable expectation that the resulting protein will have the desirable biological activity. Thus, in light of the nature of the invention, the state of the art, the high level of unpredictability in the art, the lack of direction or working examples in the specification, and the high quantity of experimentation that would be required to practice the claimed invention. The specification does not provide the requisite examples nor a representative number of different sequences that would allow the skilled artisan to produce a nucleic acid that comprises 90%,of SEQ ID NO:14 or an isolated polypeptide having 90% least 90% identity to the polypeptide of SEQ ID NO:5 that would dip[ay the

desired function, nor does the disclosure provide criteria that explicitly enable such critical features. There is no guidance in the specification as to how one of ordinary skill in the art would generate a nucleic acid or a polypeptide encoded thereby, other than that exemplified.

Therefore, one of ordinary skill in the art would not know how to make or use all of the polypeptides and polynucleotides having 90% identity to SEQ ID NO:5 or SEQ ID NO:14, respectively, as encompassed by claims 21 and 31.

Claims 23, 26-28, 29, 32 and 36 are also rejected under 35 U.S.C. 112, first paragraph, so long as they depend on claims 21 and 31 for the limitations set forth directly above.

The instant specification also fails to adequately describe an isolated polypeptide comprising an amino acid that has at least 90% identity to the polypeptide of SEQ ID NO:5, as recited in claim 21, or an isolated polynucleotide comprising at least 90% identy to the polynucleotide of SEQ ID NO: 14, as recited in claim 31. The description of one polypeptide (SEQ ID NO: 5) and one polynucleotide sequence (SEQ ID NO:14) is not adequate written description of an entire genus of functionally equivalent polypeptides and polynucleotides. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is

a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required.

Therefore, only the isolated polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 5 and the isolated polynuleotide sequence set forth in SEQ ID NO:14, but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph.

(11) Response to Argument

At p. 4, third paragraph of the Brief, Appellant characterizes the invention as a polynucleotide sequence corresponding to a gene that is expressed in human endometrium tissues, as well as the polypeptide encoded by the polynucleotide, said polypeptide identified as a human SOCS protein (HSCOP-5), which is a member of the class of SOCS proteins, which function in cell signaling. Appellant urges that the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development and diagnosis of disease, none of which requires knowledge of how the claimed polypeptide or the claimed polynucleotide actually function. Appellant argues that the fact that the claimed polypeptide is a member of the SOCS protein family alone demonstrates utility, because each of the members regardless of their particular functions is useful. Applicants further submit that there is no evidence that any member of this class of polypeptides, let alone a substantial number of them, would have no patentable utility. Applicants conclude that there is more than substantial likelihood that the claimed polypeptide, as well as the polynucleotide encoding the polypeptide, also have patentable utility, regardless of the actual function of the claimed polypeptide. Appellant states that the claimed invention already enjoys significant commercial success.

These arguments have been fully considered, but are not found persuasive, because the instant specification does not demonstrate that having homology to or being a member of SOCS protein family assures the claimed polynucleotide and the encoded polypeptide with a utility common to all the members of this family. The fact that other members of this family may have utility is irrelevant, since the physiological

relevance of the claimed nucleic acid or the encoded polypeptide must be disclosed, in order to meet the requirements under 35 U.S.C. §101. Furthermore, having an SOCS box does not impart a utility common to all proteins having this box, because, the physiological significance (which is distinct from physiological function) of the claimed sequence must be disclosed, in order for the claimed sequence to be useful diagnostically or therapeutically. A specification can meet the legal requirements of utility and enablement for a new polynucleotide as long as the specification discloses a credible, specific and substantial asserted utility for the new polynucleotide, or a well-established utility for the claimed polynucleotide. For example, if a novel polynucleotide is shown to be expressed in colon cancer and not expressed in healthy colon tissue, but there is no disclosure of the biological activity of the polypeptide encoded by the polynucleotide, said polynucleotide would not be rejected under 35 U.S.C. §§ 101 and 112, first paragraph, as it has utility and is enabled as a colon cancer marker. However, such is not the fact pattern in the instant case. Also, using the polypeptide of the instant invention for drug discovery, or for toxicology testing does not provide the claimed invention with specific or substantial utility, since any protein can be used for these general purposes. Furthermore, Applicants have failed to identify compounds toxic to the protein of the instant invention, nor organs susceptible to said toxicity. Applicants disclose that the claimed nucleic acid is expressed in cDNA libraries made from reproductive, cardiovascular, cancer-associated, inflammation and fetal tissues; however, they do not demonstrate the significance of this expression, or the role of this protein in these tissues once it is expressed. There is little doubt that, after further

characterization, and once the specific role of the protein encoded by the claimed nucleic acid is ascertained, it would have a specific, substantial and credible utility; however, further characterization is part of the invention and until it had been undertaken, the claimed invention is not supported by a specific asserted utility or a well established utility. Furthermore, evidence of commercial success, while sometimes persuasive as secondary evidence of non-obviousness, is immaterial to utility and enablement. Many products have enjoyed commercial success due to fads or clever advertising, wherein the products would not have met the legal standards for utility and enablement.

Beginning at p. 5, second paragraph, Appellants discuss the previously submitted Bedilion and Furness declarations, and characterize the declarations as describing some of the practical uses of the claimed invention in gene and protein expression profiling studies in toxicology testing, and submit that such a use would be readily apparent to the skilled artisan at the time the application was filed. At page 5, third paragraph, Appellants discuss the declarations by Dr. Rockett and a second declaration by Dr. Bedilion, a declaration by Dr. Iyer submitted with the Brief under 37 CFR 1.132, and ten scientific references filed before 25 May 1999, the priority date of the instant application. On pages 6-8, Appellants characterize the Rockett, Iyer and Bedilion declarations, and the ten references, as describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications, thus allegedly demonstrating the examiner's position to be without merit. Beginning at the paragraph 4 of p. 8 of the Brief, Appellants criticize the examiner's position that the

claimed polynucleotide and claimed polypeptide cannot be useful without precise knowledge of its biological function. However, Appellant is mischaracterizing the examiner's position. A specification can meet the legal requirements of utility and enablement for a new polynucleotide as long as the specification discloses a credible, specific and substantial asserted utility for the new polynucleotide, or a well-established utility for the claimed polynucleotide. A hypothetical example may serve to clarify. For example, a hypothetical specification discloses that a claimed polynucleotide is closely linked chromosomally to a known disease, and that there is a restriction fragment length polymorphism for the polynucleotide which co-segregates with the disease. Therefore, the polynucleotide may be used to detect individuals carrying the disease gene. The hypothetical specification does not disclose the biological activity of the polypeptide encoded by the polynucleotide. The claimed polynucleotide in the hypothetical example would not be rejected under 35 U.S.C. §§ 101 and 112, first paragraph, as it has utility and is enabled as a disease marker. However, such is not the fact pattern here. The instant specification discloses that the claimed polynucleotides and polypeptide belong to the SOCS family and hypothesizes that the protein is involved in cell signaling. There is no sufficient disclosure that the claimed polynucleotide and polypeptide are expressed at altered levels or forms in any specific, diseased tissue. Also, no evidence has been brought forth that the claimed polynucleotide and polypeptide having specific cell signaling activities.

At page 8, at paragraph 6, Appellants state that the final office action is replete with arguments made and positions taken for the first time in a misplaced attempt to

justify the rejections of the claimed invention under 35 U.S.C. §101 and 112. Appellants contend that the Examiner's new position regards the gene expression monitoring results obtained using the SEQ ID NO:14 polynucleotide or the SEQ ID NO:5 polypeptide which provide no meaningful information. The Appellants submit that the final office action fails to acknowledge that the gene microarrays disclosed in the priority Lal '104 application can be used to monitor the expression level of large numbers of genes simultaneously agents" for a number of purposes, including to develop and monitor the activities of therapeutic agents. Appellants submit three declarations filed by Drs. Rocket, Iyer and Bedilion and ten new references and argue that these were filed in response to the Examiner's new position taken in the final office action.

The declarations are admitted and the new references are being considered. However, the position taken by the Examiner regarding the use of the claimed polynucleotide in gene expression monitoring applications is not a misplaced attempt to justify the rejections of the claimed invention under 35 U.S.C. §101 and 112, but said position was taken in responding to Applicants' arguments raised in the response filed on 25 June 2003, page 14. In that response Applicants raised the issue of using the claimed polynucleotide in gene expression monitoring, in which the Examiner responded that such use is not specific because any expressed polynucleotide can be added to a microarray for gene expression monitoring.

I. The applicable legal standard

Beginning at p. 9 of the Brief, Appellants summarize case law on the utility requirement. The essential disagreement appears to be the interpretation of what

constitutes a specific, substantial and credible utility, as will be explained more fully below.

II. The use of the claimed SEQ ID NO: 14 and the encoded polypeptide for toxicology testing, drug discovery, and diagnosis of conditions characterized by expression of HSCOP-5, are alleged to be sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph.

Appellants argue at pages 11 of the Brief that the use of the claimed polynucleotide of SEQ ID NO: 14 and the claimed polypeptide of SEQ ID NO:5 for toxicology testing, drug discovery, and diagnosis and diagnosing conditions characterized by expression of HSCOP-5 are practical uses that confer specific benefits to the public. Appellants state that there is "well-established" uses for the claimed invention known to persons of ordinary skill in the art and that there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. Appellants assert that such is sufficient to establish utility for the claimed polynucleotide and the encoded polypeptide. This is not found to be persuasive. While the examiner agrees that any polynucleotide, including the claimed polynucleotides, can be used in a cDNA microarray, such does not confer patentable utility on the claimed polynucleotides. Since any polynucleotide can be used in a microarray, such a use is not specific to the claimed polynucleotides. Just as any orphan receptor can be used in an assay to screen for ligands, such does not confer patentable utility on a particular orphan receptor. Such can be done with any orphan receptor, and thus the asserted utility is not specific. Furthermore, since the specification does not disclose a

persuasive correlation between any disease or disorder and an altered level or form of the claimed polynucleotide or the claimed polypeptide, the results of gene expression monitoring assays would be meaningless without significant further research. Therefore, the asserted utility is also not substantial.

A. The claimed polypeptide's membership in the SOCS protein family demonstrates utility.

On pages 11-12, Appellants state that because there is a substantial likelihood that the claimed HSCOP-5 is a member of the family of polypeptides known as SOCS proteins, the members of which are indisputably useful, there is an implication substantial likelihood that the claimed polypeptide is similarly useful. Appellants submit that they need not show any more to demonstrate utility. Appellants continue that it is undisputed that claimed polypeptide is a protein having the sequence shown in SEQ ID NO:5 and referred to as HSCOP-5, that the they have demonstrated more than reasonable probability that it is a member of SOCS protein family which include proteins that function in cell signaling. Appellants urge that the Examiner must accept the Appellants' assertion that the claimed polypeptide is a member of the SOCS family and that utility is proven by a reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt its utility. Appellants refer to the Bedilion and Furness declarations as explaining the many reasons why a person skilled in the art reading the instant application would have understood that application to disclose the claimed polynucleotide to be useful for a number of gene expression monitoring applications,

such as a probe for expression of the polynucleotide in connection with the development of drugs and the monitoring of the activity of such drugs. The Bedilion declaration discusses microarrays and Northern analysis for measuring such. Specifically, Appellants quote from the Bedilion declaration that a person skilled in the art would have been able to use the claimed polynucleotide in expression profiling studies in toxicology. Appellants submit that that a post-filing reference confirms Applicants' prior identification of HSCOP-5 as a member of SOCS protein family, (Vasiliauskas et al disclose a protein having 100% identity to SEQ ID NO:5, which they identify as human Swip-1).

This is not found to be persuasive. The claimed polypeptide of SEQ ID NO:5 appears to have the conserved C-terminus SOCS box, although it lacks an SH2 domain that all eight known SOCS family members contain. Vasiliauskas et al. reference does disclose a protein having 100% homology to the polypeptide of SEQ ID NO:5, which is described as being a human homolog hSWIP-1. Although Vasiliauskas et al characterize a chick SWIP-1, showing that it integrates two signals originating from structures adjacent to the segmental mesoderm, the authors have not characterized the human homolog (hSWIP-1 which shares 100% homology to SEQ ID NO:5) and no function or significance have been attached to this human homolog, only that it shares 88% homology to the c-SWIP-1. Thus while the Examiner accepts Appellants' assertion that the claimed polypeptide contains the SOCS box; however, having an SOCS box does not impart a utility common to all proteins. The instant specification does not substantiate a link between the claimed polynucleotide/polypeptide and any specific

disorder. The specification merely discloses that the claimed polynucleotides are structurally related to SOCS family of proteins, and that they are expected to be involved in cell signaling. The specification also discloses that claimed nucleic acid is expressed in cDNA libraries made from reproductive, cardiovascular, cancer-associated, inflammation and fetal tissues. Many genes expressed in diseased tissues have nothing whatsoever to do with the disease and are not targets for drug development or toxicology. For example, actin and histone genes are expressed in diseased tissues; they are constitutively expressed in all tissues. These are not suitable targets for drug development or toxicology studies, since disruption of these genes would kill the patient.

B. The use of HSOP-5 and the polynucleotide encoding it for toxicology testing, drug discovery and disease diagnosis are practical uses that confer "specific benefits" to the public.

At p. 12 of the Brief, Appellants refer to the opinions of Drs. Bedilion, Furness Rockett and Iyer, that a person skilled in the art at the time of the invention would have understood that any expressed polynucleotide is useful for gene expression monitoring applications using cDNA microarrays. Appellants refer to the opinion of Dr. Bedilion, who explains in his declaration that a person of skill in the art in 28 May 1998 (the priority date for the claimed invention) would have understood that the claimed polynucleotide to be useful for gene expression monitoring applications as a highly specific probe for a the expression of that specific polynucloetide in connection with the development of drugs and the monitoring of the activity of such drugs. Appellants

further refer to Dr. Bedilion's first declaration which gives a lengthy information about gene expression monitoring applications, in particular, microarray technology.

However, using the claimed nucleic acid in gene expression monitoring does not provide the claimed invention specific utility, because no meaningful information will be obtained from tracking the level of expression of the claimed nucleotide, because there is no physiological or biological significance attached to this nucleotide or the encoded protein. Without a disclosure of a particular disease state in which the claimed polynucleotides are expressed at an altered level or form, it would be impossible to determine what the results of a gene expression monitoring assay mean. For example, if a compound is tested on a microarray comprising the claimed polynucleotides and affects expression of the polynucleotides negatively, it cannot be determined if that means that the compound is a potential good drug for a disease or would acerbate the disease if administered. The test results also would not have meaning in terms of what specific disease is relevant. The asserted utility in gene expression monitoring assays is thus not substantial, because significant further research would have to be conducted to determine which diseases correlate with altered forms or levels of the claimed polynucleotides, and whether the claimed polynucleotides are overexpressed or underexpressed in the diseased tissue. Furthermore, since any expressed polynucleotide can be added to a microarray for gene expression monitoring, the asserted utility is not specific to the claimed polynucleotides. The specification does not disclose that the claimed gene is a marker for specific diseases. Absent a disclosure of altered levels or forms of a gene in diseased tissue as compared with the corresponding

healthy tissue, the gene is not a disease marker or an appropriate target for drug discovery or toxicology testing. The fact that there is an entire industry on gene expressing technology, does not provide the claimed invention with specific or well established utility, because, this revolutionizing technology enables scientists to attain ambitious goals from identifying genetic variations associated with disease to discovering new drug targets. However, the instant application is not drawn to a novel gene chip technology, but rather to nucleic acid sequences with no known physiological role. Furthermore, evidence of commercial success, while sometimes persuasive as secondary evidence of non-obviousness, is immaterial to utility and enablement. Many products have enjoyed commercial success due to fads or clever advertising, wherein the products would not have met the legal standards for utility and enablement. Beginning at paragraph 3 of page 15, Appellants refer to the opinion of Dr. Rockett, who explains in his declaration that there are a number of other differential expression analysis technologies that preceded the development of microarrays, some by decades, and that have been applied to drug metabolism and toxicology research, and which are listed in the first paragraph. It is not disputed that one of ordinary skill in the art would agree that such differential expression analysis technologies including cDNA microarray technology are extremely valuable techniques, and that these were well-established utilities at the time of filing. However, the claims are not drawn to the various techniques or to a microarray. The claims are directed to a specific polynucleotide and the encoded polypeptide. Any polynucleotide that would be added to a microarray would increase the value of that microarray and possibly show altered expression due

to treatment with a potential drug target directed to a different polynucleotide (or the encoded protein), or be a part of a microarray that demonstrates differences in hybridization patterns in a particular disease state. Therefore, this asserted utility would be applicable to any polynucleotide and does not rely on any specific attribute of the polynucleotide, and thus the asserted utility for the particular polynucleotide claimed is not specific, substantial or well-established.

At paragraph three on page 14 Appellants state that nowhere does the Patent Examiner address the fact that, as described on page 44, lines 10-22 and page 53, lines 1-21 of the instant specification, the claimed polynucleotides can be used as highly specific probes in for example, cDNA microarrays, and the claimed invention is not, in that regard, some random sequence whose value as a probe is speculative or would require further research to determine. The use of the claimed polynucleotide in gene expression monitoring applications was discussed in the Final Office Action mailed on 21 October 2003, pages 5-7, as not being a specific or substantial utility.

Beginning at the last paragraph on p. 15 of the brief, Appellant argues that, given that the claimed polynucleotide is known to be expressed, its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. Appellant reviews case law pertinent to the patentable utility of research tools. This is not found to be persuasive. Appellant's analogy is misplaced. It is true that a scale has patentable utility as a research tool. However, the object being weighed on the scale does not necessarily have patentable utility. In the instant case, microarray technology has patentable utility. However, the microarray is not being

claimed, but rather a polynucleotide that can be used in microarrays. The claimed polynucleotide is not disclosed as being expressed at an altered level or form in any diseased tissue as compared to the corresponding healthy tissue. Therefore, the assertion that the claimed polynucleotide has patentable utility as a probe in, or member of, a microarray is not specific. Any orphan polynucleotide can be used in the same way.

At pages 16-18, Appellants argue that literature reviews published shortly before the filing of the LAL '104 application (28 May 1998) describing the state of the art further confirm the claimed invention's utility. Appellants discuss U.S. Patent No. 5,807,522 (Brown '522 Patent), which issued from a patent application filed on June 1995, and published 29 December 1995, shows that the patent office recognizes the patentable utility of the cDNA technology developed in the early to mid 1990s. This is not found persuasive. The patentability of the cDNA technology is not disputed, however, the claimed invention is not drawn to this revolutionizing technology which enables scientists to attain ambitious goals from identifying genetic variations associated with disease to discovering new drug targets. The instant invention is not drawn to a novel gene chip technology, but rather to a nucleic acid sequence and the encoded polypeptides with no known physiological role.

Appellants refer to Rockett et al. which explains that the claimed invention is useful for differential expression analysis regardless of how expression is regulated (Xenobiotica article, and Rockett Declaration, Exhibit C), and explains the recognition of the importance of differential gene expression and characterization, that differential

expression technologies are applicable to a broad range of models and do not require any prior knowledge of the specific gene which are up or down regulated, and that the current use of gene profiling yields a pattern of gene changes for a xenobiotic of unknown toxicity which may be matched to that of well characterized toxins, thus alerting the toxicologist to possible in vivo similarities between the known and the standard, thus providing a platform for more extensive toxicological examination. On page 17 Appellants present another pre-September 1998 article, Lashkari et al., which explicitly states that predicted Open Reading Frames (ORFs) have numerous uses, such as by arraying onto glass for expression analysis. These are not persuasive. The Examiner notes that these references, e.g. Rockett et al. and Lashkari et al. have not been previously cited or discussed on the record, nor have they been made of record by appellants in any information disclosure statement. The Rockett et al. paper (Xenobiotica 1999, 2947):655-691), however, supports the Examiner's assertion that the use of the claimed nucleic acids in microarrays does not meet the requirement of being specific and substantial. In the abstract of the paper, Rockett et al. state ***"An important feature of the work of many molecular biologists is identifying which genes are switched on and off in a cell under different environmental conditions or subsequent to xenobiotic challenge. Such information has many uses, including the deciphering of molecular pathways and facilitating the development of new experimental and diagnostic procedures.'*** **(Emphasis added).** In essence, Rockett is teaching that the purpose of such "open" microarrays, wherein the function of the specific nucleic acids is unknown, as is the case for SEQ ID NO: 14, is that the results

of the experiment are to be used to decipher molecular pathways, and facilitate the development of other experimental or diagnostic procedures. Such would seem to the Examiner to clearly fall under the category of use for further experimentation to determine the properties of that which is being claimed, in this case the further experimentation being to develop other procedures that would take advantage of the knowledge gained by the initial experiment, or to 'decipher' molecular pathways. Thus, it is clear from Rockett et al. that, as asserted above by the Examiner, that the use of the claimed polynucleotide in either microarrays or in gene expression monitoring merely constitutes further research to determine the significance of the claimed nucleic acid itself; if the results of such experiments demonstrated that the claimed sequences were or were not present under particular conditions, such would be an invitation to experiment to determine why, which would fall under the aegis of further experimentation to determine the properties of that which is being claimed. Similarly, the Lashkari et al. publication, by appellant's admission a pre-filing date reference that has not been previously cited, does not support appellant's assertions: While Lashkari et al. indeed teach that "amplicons", or portions of DNA amplified from the genome by PCR can be used by arraying onto glass for expression analysis, the entire context of the article has been ignored by appellants: The very first paragraph of the paper states "This massive and increasing amount of sequence information allows the development of novel experimental approaches to identify gene function." The paragraph bridging the columns of that page starts "Experimental analysis must be performed to thoroughly understand the biological function of a gene product." The same paragraph states "it is

clear that novel strategies are necessary to efficiently pursue the next phase of genome projects- whole-genome experimental analysis to explore gene expression, gene product function, and other genome functions (emphasis added)." Thus, Lashkari et al. are clearly teaching that sequences of unknown function or significance are used in such strategies to learn more about the sequences themselves and the genes they represent. The Examiner maintains that this is clearly further research of the type that is not sanctioned as fulfilling the requirements of 35 U.S.C. § 101. Nuwaysir et al newly cited and argued by Appellants, clearly shows that to be useful in a toxicology screen, one of ordinary skill in the art would want to know what kind of gene one was using; table 1, cited by appellants, clearly shows that one would first identify the function of the gene in the cell prior to using it in such a toxicology screen. No such identification has been performed for the nucleic acid of SEQ ID NO: 14.

C. The use of nucleic acids coding for polypeptides expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is alleged as "well-established".

Beginning at p. 18 of the Brief, Appellants argue that the claimed polynucleotides are useful as tools for toxicology testing, drug discovery, and the diagnosis of disease and that these uses are "well-established". Each of these uses will be addressed individually, because the facts and issues directed to each use are distinct and separable. First, Appellant argues that toxicology testing is a well-established utility and concludes that the claimed polynucleotides could be used in this manner and that the claimed invention possesses utility, as described by Furness, Bedilion, Rockett and Iyer

in their declarations, and cite a section on page 656 of the Rockett Declaration which explains that early identification of toxic drug candidates can shorten the development process and contribute substantially to the safety assessment of new drugs. Appellants also present two references, Nuwaysir et al. (reference 2) and Steiner and Anderson (reference 3) that teach the same, and cite Nuwaysir which describes a Human ToxChip containing 2089 human clones which were selected for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. On page 13 of the Brief Appellants argue that the more genes that are available for use in toxicology testing, the more powerful the technique and cite from Rockett and Dix (reference 4) that "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." Appellants also present an email from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, was well as the original message to which she was responding (reference No. 5), indicating that even the expression of carefully selected control genes can be altered. Appellants also argue that there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

The e-mail referenced by appellants at page 13 of the Brief, also new to the prosecution, is not sufficiently legible to allow thorough analysis. However, it would seem to indicate that Ms. Afshari is in the process of designing chips to be used in toxicology screens, and is performing substantially more characterization of the expression patterns of candidate sequences than is disclosed in the specification at

hand. Thus, the e-mail would seem to indicate that while the nucleic acid of SEQ ID NO: 14 might be useful in a toxicology chip such as those allegedly designed by Ms. Afshari, it would require substantial further research to determine such. Utility must be in readily available form, and utility of SEQ ID NO: 14 in a toxicology screen does not appear to meet that burden. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct,.1966).

Appellants present sections of publications U.S. Pat. No. 5,569,588 (reference 9e), WO 95/21944 (reference 9a), WO 95/20681 (reference 9b) (5,840,484, 6,114,114, 6,303,297) and WO 97/13877 (reference 9g) are provided on pages 20-28 of the Brief, that allegedly provides further evidence of the well-established utility of all expressed polypeptides and polynucleotides in toxicology testing. On pages 20-22 of the Brief, Appellants present sections of WO 95/21944, which describes the use of microarrays in expression profiling analyses and that patterns of expression can be used to distinguish healthy tissues from diseased tissues and that patterns of expression can additionally be used in drug development and toxicology studies, without the knowledge of the biological function of the encoded gene product. On pages 22-24, Appellants present sections of WO 95/20681, which has three issued U.S. counterparts, U.S. Pat. Nos. 5,840,484, 6,114,114 and 6,303,297, which describes the use of transcript expression patterns, or images, each comprising multiple pixels of gene-specific information for diagnosis, for cellular phenotyping, and in toxicology and drug development efforts, using a plurality of methods for obtaining the expression data, one of which is microarray hybridization. On pages 25-27, Appellants present sections of U.S. Pat. No.

5,569,588, which describes an expression profiling platform, the "genome reporter matrix", which is different from nucleic acid microarrays, and which also describes the use of nucleic acid microarrays and makes clear that the utility of comparing multidimensional expression data sets is independent of the methods by which such profiles are obtained, and that such expression analysis is useful in toxicology, particular pointing out that a gene's failure to change in expression level is a useful result. At paragraph 5 on page 27, Appellants argue that the August 11, 1997 press release from the '588 patent's assignee, Acacia Biosciences (now part of Merck) (reference 9h), and the September 15, 1997 news report by Glaser in Genetic Engineering News (reference 9i), attest to the commercial value of the methods and technology described and claimed in the '588 patent. On pages 27-29 of the Brief, Appellants present sections of WO 97/13877, which describes an expression profiling technology differing somewhat from the use of cDNA microarrays and differing from the genome reporter matrix of the '588 patent, but the use of the data is analogous. The reference describes use of expression profiling in toxicity determinations. On pages 28-29 Appellants state that the potential benefit to the public in terms of lives saved and reduced health costs, are enormous. Appellants provide evidence of the benefits of this information, in which CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology and other information to identify the key gene associated with Tangiers disease, and state that other customers have reduced the time associated with target discovery and validation, and that over 50 percent of the drug targets in its current pipeline of another customer were derived from the Incyte database, and by

doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs. Appellants further assert that because the Examiner has failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be overturned regardless of their merit.

The references and arguments have been carefully considered but are not persuasive. For a utility to be "well-established" it must be specific and substantial. In this case, as indicated at pages 20-29 of the Brief, all nucleic acids and genes are in some combination useful in toxicology testing. However, the particulars of toxicology testing with the claimed polynucleotides are not disclosed in the instant specification. Neither the toxic substances nor the susceptible organ systems are identified. Therefore, this is a utility which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA, but is only potential with respect to the claimed polynucleotides. Because of this, such a utility is not specific and does not constitute a "well-established" utility. Further, because any potential diagnostic utility is not yet known, the utility is not substantial because it is not currently available in practical form. Moreover, use of the claimed polynucleotide in an array for toxicology screening is only useful in the sense that the information that is gained from the array is dependent on the pattern derived from the array, and says nothing with regard to each individual member of the array. Again, this is a utility which would apply to virtually every member of a general class of materials, such as any collection of proteins or

DNA. Even if the expression of Appellant's individual polynucleotides or polypeptides are affected by a test compound in an array for drug screening, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this consideration, the individually claimed polynucleotides and polypeptides have no "well-established" use. The artisan is required to perform further experimentation on the claimed material itself in order to determine to what "use" any expression information regarding this nucleic acid could be put.

The supplied references and Appellants' arguments have been fully considered but are not deemed persuasive. As discussed above, the use of genomic information databases and microarray technologies are valuable and were well-established at the time of filing of the instant application. There is also no doubt that using such databases and technologies is very useful in discovering genes associated with diseases, or in drug discovery or toxicology testing. However, the utilities are well-established for entire databases or microarrays containing many polynucleotides, but the claims are drawn to specific polynucleotides, not the databases and techniques. The claimed polynucleotide or the encoded polypeptide has not been disclosed as being associated with any particular disease or condition by its being expressed at an altered level or form in diseased tissue as compared to the corresponding healthy tissue. Thus, this asserted utility is not specific. Determining the relationship between the claimed polynucleotides and any specific disease or disorder would require significant further research. Therefore, this asserted utility is also not substantial. In the absence of any disclosed relationship between the claimed polynucleotide or the protein

that is encoded thereby and any disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

Because any polynucleotide could be used in the methods of the asserted utilities, the claimed polynucleotide does not have a specific, substantial and well-established utility. An analogous utility to that asserted by Applicants would be extracting mRNA from a tissue sample, electrophoresing the mRNA on a polyacrylamide gel, transferring to a membrane and hybridizing with a nucleic acid probe specific to that polynucleotide. It is well-established that any polynucleotide may be used in a method of hybridization to determine for example, the expression of the polynucleotide in various tissues, but this does not confer a well-established utility to the polynucleotide itself.

With regard to drug discovery and development, Appellants mention expression profiling as one use of the claimed polynucleotide. Appellants refer to recent developments as providing evidence that the benefits of this information are already beginning to manifest themselves. However, Appellant is incorrect in asserting that the efficacy (ability of producing a desired effect) of a compound could be evaluated from the result of a transcript image because there is no way to assess the meaning of any individual hit obtained from this procedure. The first requirement is that one must know

the biological significance of the polynucleotide(s) which is (are) being evaluated. Without this information, the results of the transcript image are useless because one would not know if the polynucleotide expression should be increased or decreased or even what significance could be attributed to such changes in expression profiles.

With regard to diagnosis of disease, in order for a polynucleotide to be useful, as asserted, for diagnosis of a disease, there must be a well-established or disclosed correlation or relationship between the claimed polynucleotide and a disease or disorder. The presence of a polynucleotide in tissue that is derived from cancer cells is not sufficient for establishing a utility in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed cDNA and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polynucleotide to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the claimed polynucleotide is either present only in cancer tissue to the exclusion of normal tissue or is expressed in higher levels in diseased tissue compared to normal tissue (i.e. over expression). Evidence of a differential expression might serve as a basis for use of the claimed polynucleotides as diagnostics for diseases. However, in the absence of any disclosed relationship between the claimed polynucleotides or the proteins that are encoded thereby and any disease or disorder and the lack of any correlation between the claimed polynucleotides or the encoded proteins with any known disease or disorder, any information obtained

from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

D. The uncontested fact that the claimed polynucleotide encodes a protein in the SOCS protein family is also asserted to demonstrate utility.

At p. 29 of the Brief, Appellants argue that the claimed polynucleotide encodes for a protein having the sequence shown in SEQ ID NO:5, referred to as HSCOP-5, which is a member of SOCS family. Appellants argue that the utility of the claimed polynucleotide can be imputed based on the relationship between the protein of SEQ ID NO: 5, which has been demonstrated to be a member of the SOCS family, and that the SOCS family of proteins SOCS family members function in cell signaling. Appellants state that the Patent Examiner does not dispute any of the facts set forth on page 29, or that if a polynucleotide encodes for a protein that has a substantial, specific and credible utility, then it follows that the polynucleotide also has a substantial, specific and credible utility. Appellants also assert on page 29 that the Examiner must accept the Applicant's demonstration that the polypeptide encoded by the claimed invention is a member of the SOCS family and that utility is proven by a reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility (*In re Langer*), and the Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary. Appellants

also assert that the Examiner has not provided any evidence that any member of the SOCS family, let alone a substantial number of those members, is not useful, and in such circumstances, the only reasonable inference is that the polypeptide encoded by the claimed invention must be, like the other members of the SOCS family, useful.

This argument is not found to be persuasive because evidence that having an SOCS box does not impart a utility common to all proteins having this box has been brought forth. Although the protein of the instant invention contains an SOCS box, it is not predictable what the function of any SOCS protein is from this information. Whereas a broad class of enzyme such as the ligases have a general utility in such an application as ligation of DNA for cloning purposes which is essentially applicable to all of the members of that class, however, having an SOCS box does not impart a utility common to all proteins having this box. Suppressor of cytokine signaling family (SOCS) are recently identified inhibitors of cytokine and growth factor signaling that act through Janus kinase (JAK)/signal transducers and activators of transcription pathway. To date there are eight SOCS family members (CIS1, SOCS1-SOCS7), and all eight members contain a central SH2 domain and a conserved C-terminal motif of 40 amino acid residues, (see Gisselbrecht, Sylvie, European Cytokine Network, Vol.10, No.4, pages 463-470, especially page 464). The SH2 domain of CIS, SOCS-1 and SOCS-3 (the most extensively studied members), is required for the inhibition of cytokine response by these molecules indicating. Although the claimed polypeptide of SEQ ID NO:5 appears to contain the SOCS box, it does not contain the SH2 domain which seems to be an important structural feature for the actions of some of the members of the SOCS

family members.. Other proteins that contain SOCS box contain WD-40 repeats, a SPRY domain or ankryn-repeat or GTpase domain N-terminal of the SOCS box, (see Hilton et al page 1 14, column 2 and figure 1). Thus it is unclear from the instant specification which group of SOCS box containing proteins does the claimed polypeptide belong to. It is thought that SOCS- 1 plays an important role in regulating signal transduction by binding via its SH2 domain to activated JAK molecules and that CIS is thought to block STATS. However, the roles that other members of this family play have not been elucidated. Although the conservation of the SOCS box at the amino acid level appears to be important, its function is not known at the moment, (see Hilton, page I 18, bottom of column 1) and it seems that SOCS-I; does not act through the SOCS box to bind to JAK. Therefore, having an SOCS box does not impart a utility common to all proteins having this box. Furthermore, without knowing the biological significance of the claimed polypeptide, what other domains does it contain, (for example does it contain an SH2 domain which seems important for SOCS-I, does the claimed protein regulate signal transduction and if so how?), one of ordinary skill in the art would not be able to use them or predict an activity for said protein, simply because it belongs to this family of proteins. The M.P.E.P., 2107.01 states:

"A "specific utility" is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention."

The nucleic acids of the instant invention falls into this category.

E. Objective evidence is alleged to corroborate the utilities of the claimed invention.

Beginning at bottom of p. 29 of the Brief, Appellants argue that a "real-world" utility exists if actual use or commercial success can be shown. Citing case law, Appellant urges that such a showing is conclusive proof of utility. Appellant argues that a vibrant market has developed for databases containing all expressed genes, including those of Incyte, the real party at interest in the instant appeal. Appellants urge that Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven valuable, and that the databases including the claimed polynucleotide would be even more valuable. Appellant's arguments have been fully considered but are not deemed to be persuasive. The case law indicates that a rejection under 35 U.S.C. § 101 *for lack of operability* can be overcome by a showing of actual use or commercial success. The instant issue is whether or not the asserted utilities meet the three-pronged test for credibility, specificity, and substantiality. Such is not necessarily addressed by a showing of commercial success or actual use. As argued previously, many products which lack patentable utility enjoy commercial success, are actually used, and are considered valuable. These include silly fads such as pet rocks, but also include serious scientific products like proteins with no known physiological role.

III. The patent examiner's rejections are alleged as being without merit

A. The precise biological role or function of an expressed polynucleotide is alleged as being not required to demonstrate utility

Beginning at p. 31 of the Brief, Appellant characterizes the examiner's rejection as being based on the grounds that, without information as to the precise biological role of the claimed invention, the claimed invention lacks specific patentable utility. Appellant characterizes the examiner's position as it is not enough that a person skilled in the art could use and would want to use the claimed invention either by itself or in a microarray, but that Appellant also is required to provide a specific and substantial interpretation of the results generated in a given expression analysis. Appellant argues that specific and substantial interpretations regarding biological function may be required by technical journals, but are not necessary for patents. Appellants urge that the relevant question is not how or why the invention works, but whether the invention provides an identifiable benefit. Appellants argue that the present invention meets this test. Appellants argue that the threshold for patentable utility is low. Appellant urges that only throwaway utilities are insufficient, and that knowledge of biological function is not required. This is not found to be persuasive, as it mischaracterizes the examiner's position. The rejection never states that the precise biological role of a polynucleotide is required for it to possess patentable utility. If a polynucleotide is disclosed as being linked to a known disease or disorder, even if nothing is known or hypothesized about the activities of the encoded polypeptide, then the polynucleotide has patentable utility as a disease marker. However, if a specification does not disclose such information, as is the case here, then there is no patentable utility. If a compound causes the claimed

polynucleotide to be expressed at a decreased level in a microarray, does that mean the compound is a potential drug or a potential toxin? That determination requires significant further research, and thus the asserted utility is not substantial. Also, any expressed polynucleotide *can* be used in a microarray; thus the unasserted utility is also not specific.

B. Membership in a class of useful products is asserted to demonstrate utility.

Beginning at p. 32 of the Brief, Appellants assert that the examiner improperly refused to impute the utility of the SOCS family to the claimed invention. Appellants urge that the case law requires only that the class not contain a substantial number of useless members. Appellant urges that the examiner has treated SOCS family as if the general class in which it is included is not the SOCS protein family, but rather all polynucleotides or all polypeptides, and thus not pre-selected by nature to be useful. Appellants assert that while these "general classes" may contain a substantial number of useless members, the SOCS family does not. Appellants conclude that the examiner has not presented any evidence that the SOCS class of signaling molecules has any, let alone a substantial number, of useless members, and that the examiner must conclude that there is a "substantial likehood" that the protein of SEQ ID NO: 5 encoded by the claimed polynucleotide is useful. This is not found to be persuasive. The instant specification demonstrates that the claimed polypeptide of SEQ ID NO:5 contains an SOCS box, however, it does not disclose whether the claimed polypeptide contains other structural features such as SH2 domain, a SPRY domain, an ankryn-repeat or GTpase domain N-terminal of the SOCS box which seems to be important structural

features for some of the members of this family, nor does it disclose what role in cell signaling does the claimed polypeptide play, or which signals it may inhibit.

C. Because the uses of the claimed polynucleotide in toxicology testing, drug discovery, and disease diagnosis are asserted as practical uses beyond mere study of the invention itself, the claimed invention is alleged to have utility.

At p. 33-35 of the Brief, Appellants argue that the rejection is incorrectly based on the grounds that the use of an invention as a tool for research is not a substantial use. Appellants urge that the data generated in gene expression monitoring using the claimed polynucleotide or the claimed polypeptide as a tool are not used merely to study the claimed polynucleotide or polypeptide but rather to study properties of tissues, cells and potential drug candidates and toxins. This is not found to be persuasive. As discussed above, whereas a scale or a microarray or a gas chromatograph has patentable utility as a research tool, the objects being evaluated with those research tools do not necessarily have patentable utility. In the instant case, the claimed polynucleotide is not disclosed as having a specific activity, or having any property that can be specifically useful. The claimed invention is, in fact, the object of further study, merely inviting further research. None of the utilities asserted for the claimed polynucleotide meets the three-pronged test of being specific, substantial and credible.

IV. The patent examiner is alleged to have failed to demonstrate that a person skilled in the art would reasonably doubt the utility of the claimed invention.

A. Biological function, differential expression or disease association is irrelevant to utility.

Beginning at p. 35-36 of the Brief, Appellants argue that the Examiner continues to ignore other utilities discussed in the specification and/or are well known in the art, such as toxicology testing. Appellants contend that the fact the additional experimentation could be performed to determine the biological function, disease association or differential expression of the claimed polynucloetide and the encoded polypeptide of SEQ ID NO:5 does not preclude and, is in fact, irrelevant to the actual utility of the invention, which exists today. Appellant refers to Rockett Declaration which explains that monitoring the expression of the claimed polynucleotide or the claimed polypeptide gives important information on the potential toxicity of a drug that is specifically targeted to any other polypeptide, regardless of the biological function. This is not found persuasive, because the particulars of toxicology testing with the polynucleotides and polypeptide of the instant invention are not disclosed in the instant specification. Neither are toxic substances nor susceptible organ systems identified. Therefore, this is a utility, which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA; therefore, such a utility is not specific and does not constitute a "well-established" utility.

B/C Utility of all expressed polynucleotides and expressed polypeptides in toxicology testing.

At the bottom of pages 36-38, Appellants state that the Examiner's arguments regarding the Bedilion and Furness Declarations amount to nothing more than disagreements. At page 37, the Appellants urge that the Examiner must accept Appellants' assertions to be true. The Appellants argue that monitoring the expression

of the SEQ ID NO:14 polynucleotide and the polypeptide of SEQ ID NO:4 (the polypeptide of SEQ ID NO:5 is the claimed polypeptide), is a method of testing the toxicology during drug development. Appellants contend that the Examiner has refused to consider that the claimed polynucleotide or claimed polypeptide is useful for measuring the toxicity of drug candidates which are targeted not to the claimed polynucloetide or claimed polypeptide, but to other polynucletoides or polypeptides. This is not found persuasive, because the use of the claimed polynucletoide or the claimed polypeptide in toxicity of drug candidates which are targeted to other polynucloetides or other polypeptides is not "specific", since any protein or DNA can be used in such a manner. Again, the use of the claimed polynucleotide in gene monitoring applications does not afford the claimed invention "specific utility", because this is a utility which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA. Even if the expression of Appellant's individual polynucleotides or polypeptides are affected by a test compound in an array for drug screening, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this consideration, the individually claimed polynucleotides and polypeptides have no "well-established" use. The artisan is required to perform further experimentation on the claimed material itself in order to determine to what "use" any expression information regarding this nucleic acid could be put. There is little doubt that, after further characterization, and once the specific function and role of the protein encoded by the claimed nucleic acid is ascertained, it would have a specific, substantial and credible utility; however, further characterization

is part of the invention and until it had been undertaken, the claimed invention is not supported by a specific asserted utility or a well-established utility.

D. Appellants' Invention has Specific Utility

Appellants on pages 39-40 of the Brief further assert that the submission of additional facts overcomes the concern that the asserted utility for the claimed polynucleotides is specific and substantial or a well-established utility, and that each gene on a high density spotted microarray when probed provides a signal that is specific to the cognate transcript, and that each additional probe makes an additional transcript newly detectable by the microarray, increasing the detection range, and thus versatility, of the analytical device for gene expression profiling, and increasing the resolving power of the device. Applicants state on the record that the specificity of nucleic acid hybridization was well-established far earlier than the development of high density spotted microarrays in 1995, and indeed is the well-established underpinning of may, perhaps most, molecular biological techniques developed over the past 30-40 years.

This is not found to be persuasive. Any polynucleotide is a highly specific probe for itself or its complement, or any mRNA that can be transcribed from it. Such can be said for any polynucleotide. Thus, this asserted utility is not specific. Because any polynucleotide could be used in the methods of the asserted utilities, the claimed polynucleotide does not have a specific, substantial and well-established utility. An analogous utility to that asserted by Applicants would be extracting mRNA from a tissue sample, electrophoresing the mRNA on a polyacrylamide gel, transferring to a

membrane and hybridizing with a nucleic acid probe specific to that polynucleotide. It is well-established that any polynucleotide may be used in a method of hybridization to determine for example, the expression of the polynucleotide in various tissues, but this does not confer a well-established utility to the polynucleotide that is probed and detected by this method.

IV. By requiring the patent applicant to assert a particular or unique utility, it is alleged that the patent examination utility guidelines and training materials applied by the patent examiner misstate the law.

At p. 40-41 of the Brief, Appellant challenges the legality of the Patent Examination Utility Guidelines. Since an Examiner has no authority to comment on the legality of the Guidelines, this issue will be reserved for ruling by the Board of Patent Appeals and Interferences.

Issue 2: Enablement Rejection of claims 21-29, 31-32, 36-37 with respect to the utility Rejection.

As Appellant indicates at p. 42 of the Response, a rejection under § 112, first paragraph, may be affirmed on the same basis as a lack of utility rejection under § 101. See, e.g., In re Swartz, 56 USPQ2d 1703 (Fed. Cir. 2000); In re Kirk, 153 USPQ 48 (CCPA 1967). Therefore, for reasons set forth above, Appellants' arguments and exhibits have been fully and carefully considered, but are not considered sufficient to rebut the prima facie case of lack of utility and it is believed that the rejections should be sustained.

Issue 3: Enablement Rejection of claims 21, 23, 26, 27, 31, 32 and 36 with respect to polynucleotide variants and polypeptide variants.

I. How to make

At page 42, Appellants contend that SEQ ID NO:5 and SEQ ID NO:14 are specifically disclosed in the instant application, so are variants of SEQ ID NO:5 and SEQ ID NO:14. Appellants submit that the polypeptide variant sequences and polynucleotide variant sequences are described by their being "naturally occurring" and by their percentage sequence identity with SEQ ID NO:4 and SEQ ID NO:14. Applicants contend that the instant specification teaches how to find polynucleotide variants and express them to make the polypeptide variants. Thus, Applicants contend that the making of the claimed variants by recombinant methods is disclosed in the instant specification. This is not found persuasive, because it is well-known in the prior art that changes in a nucleotide sequence can have a dramatic affect on the protein product encoded by the sequence, and that changes in the amino acid would also change the function of the protein. While the degeneracy of the genetic code accommodates some variation in the nucleotide sequence, the extent of variation disclosed go far beyond alternate codons for the same amino acid. A skilled artisan would expect that the variation in the polynucleotide sequence would at best code for a polypeptide that has impaired function and at worst be either nonfunctional or an entirely different product from that of the claimed invention. Therefore, it would be impossible to predict with certainty the effect of a substitution, insertion, or deletion of a series of nucleotides, or even one nucleotide, on the encoded product. In order to make an accurate assessment of the modifications encompassed by these claims and to determine the function of the encoded protein would require undue experimentation.

With respect to amino acid modifications, the instant specification does not provide the guidance needed to predictably alter by 10%, i.e. 42 amino acids in SEQ ID NO:5, with any reasonable expectation that the resulting protein will have the desirable biological activity.

II. How to Use

At page 44, Appellants urge that the polypeptide variants and the polynucleotide variants are useful for the same purposes as the polypeptide of SEQ ID NO:5 and polynucleotide of SEQ ID NO:14, respectively. These utilities are described under the rejection under §101 of this Appeal Brief, in the previously filed Bedilion and Furness Declarations and the currently submitted Rockett, Iyer and second Bedilion Declaration.

Appellants' arguments and exhibits have been fully and carefully considered, but are not considered sufficient to rebut the *prima facie* case of lack of utility and it is believed that the rejections should be sustained.

III Summary

Appellants conclude that the Examiner has not made a prima facie case for non-enablement with respect to the recited polynuceotides and polypeptides. Contrary to Appellants' conclusion, a *prima facie* case was made for a lack of enablement for the claimed invention, because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth above, because one skilled in the art clearly would not know how to use it.

Appellants further conclude that the recited fragments and variants of SEQ ID NO: 1 and SEQ ID NO: 2 are sufficiently described in chemical and structural terms that

the skilled artisan would recognize applicants' possession of them at the time the application was filed.

Issue 4: Written Description Rejection of Claims 21, 23, 27, 31, 32 and 36

On page 45-46, Appellants assert that an isolated polynucleotide having 90% identity to SEQ ID NO: 14 and an isolated polypeptide having 90% identity to SEQ ID NO:5, are adequately described in accordance with 35 U.S.C. § 112, first paragraph and supported by relevant case law, and cite case law and the Patent and Trademarks Office's own "Guidelines for Examination of Patent Applications Under 35 U.S.C. Sec. 112, para. 1", published Jan. 5, 2001. Appellants argue that the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well-known to one skilled in the art, and that SEQ ID NO: 14 and SEQ ID NO: 5 are specifically disclosed in the instant specification, as are variants of the sequences, and that the chemical and structural features of SEQ ID NO: 14 are described. Given SEQ ID NO: 14 and SEQ ID NO:5, one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO: 14 or SEQ ID NO:5 having at least 90% sequence identity to SEQ ID NO: 14 or SEQ ID NO:5.

This is not found persuasive, because to provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial

structure in the form of a recitation of specific fragments or percent identity. As far as the claims encompass a polypeptide sequence having a certain percent identity to SEQ ID NO: 5, there is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

I. The present claims specifically define the claimed genus through the recitation of chemical structure.

At page 47, Appellants assert that the Examiner's position that the subject matter is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, is believed to present a misapplication of the law. On page 47, Appellants cite Fiers v. Revel, and argue that if a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, then a description also requires that degree of specificity. Appellants on pages 47-49 cite University of California v. Eli Lilly and Co., and Lilly, and submit that in those cases, nucleic acids that were defined on the basis of potential methods of isolating DNA or functional characteristics did not comply with the written description requirement of 35 U.S.C. § 112, first paragraph, and assert that the claims at issue in the present application define polynucleotides and polypeptides in terms of chemical structure, rather than functional characteristics, and therefore the claims of the subject application are fundamentally different from those found in Lilly and Fiers. Appellants

assert that there is no reliance merely on a description of functional characteristics of the polynucleotides or polypeptides recited by the claims, and that by failing to base its written description inquiry "on whatever is now claimed", the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in Lilly and Fiers. These arguments are not found persuasive, because to provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof, which were considered and discussed in the analysis of the claims.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id at 1170, 25 USPQ2d at 1606."

A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, a single isolated polypeptide sequence SEQ ID NO: 5 and a single

isolated poluynucleotide sequence of SEQ ID NO:14, and discusses how variants may be obtained, and it cannot be established that a representative number of species have been disclosed to support the genus claim based on a single sequence.

II. The present claims allegedly do not define a genus which is "highly variant".

On pages 49-50, Appellants argue that the claims at issue do not describe a genus which could be characterized as highly variant, and submit the reference of Brenner et al. as evidence illustrating that the claimed genus is of narrow scope. Brenner teaches that 30% identity is a reliable threshold for establishing evolutionary homology between sequences aligned over at least 150 residues, and that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. Appellants argue that in accordance with Brenner et al., naturally occurring molecules may exist which could be characterized as SOCS proteins and which have as little as 40% identity over at least 70 residues to SEQ ID NO: 5, and the variant language of the present claims, recite for example, polynucleotides encoding "an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 5", and that this variation is far less than that of all potential SOCS proteins related to SEQ ID NO: 5.

This is not considered persuasive, because instant specification only describes the polypeptide comprising the amino acid sequence set forth in SEQ ID NO:5 and the nucleic acid of SEQ ID NO:14, but fails to describe the structure of any variant to either of these products. Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. Furthermore, the courts have held that a patentee of a biotechnological invention cannot

necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See Enzo Biochem II, 323 F.3d at 965; Regents, 119 F.3d at 1568. The court has also held that a description of DNA "'requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention." . Fiers v. Revel, 984 F.2d 1164, 1170 [25 USPQ2d 1601] (Fed. Cir. 1993)).

3. The state of the art at the time of the present invention is asserted to be further advanced than at the time of the Lilly and Fiers applications.

On page 49-50, Appellants assert that in the Lilly and Fiers cases, the parties claimed benefit of priority from 1977 and 1979, respectively, and thus the written description inquiry in those cases was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology. Appellants argue that the present application has a priority date of Sept. 17, 1998, and with the remarkable advances in recombinant DNA technology in the 20 or more years from the time of filing of the applications in Lilly and Fiers, one of skill in the art would recognize that, given the sequence information of SEQ ID NO: 14 and SEQ ID NO:5, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polynucleotide variants at the time of filing of this application. This is not found persuasive because although recombinant DNA technology has advanced tremendously since the time of Lilly and Fiers, the case law pertaining to written description requirement still requires that to provide evidence of possession of a

claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus, which factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. Because the instant application only discloses one polypeptide sequence, and the claims do not recite any function, the written description has not been met.

Summary/Conclusion

Appellants summarize their arguments on pages 50-52, which have been addressed in the response above.

On pages 50-51, Appellants submit that the final office action failed to base its "written description inquiry on what is now claimed", and since the instant claims differ those found not to satisfy the written description requirement in cases such as *Lilly* and F*iers,* the reasons cited above in response to the rejection of claims under 35 U.S.C. § 112, first paragraph, must be overturned. Also Appellants submit that for the reasons cited above in response to the rejection of claims under 35 U.S.C. § 101/112, these rejections are improper and should be reversed. Applicants' arguments have been fully considered but are not deemed persuasive, for reasons of record in the previous Office Actions, mailed on 21 February 2003 and 21 October 2003, and for the reasons discussed under 35 U.S.C. § 112 in the present action.

For the above reasons, it is believed that the rejections should be sustained.

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